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White Paper AGA: Drug Development for Eosinophilic Esophagitis

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Since first characterized in 2 small case series in the early 1990s, eosinophilic esophagitis (EoE) has emerged as a commonly identified cause of esophageal symptoms in children and adults.[1,2] Although several highly effectively dietary, pharmacologic, and endoscopic therapies have been reported, none is currently approved by either the US Food and Drug Administration (FDA) or European regulatory authorities. Evolving diagnostic criteria have challenged drug development, in particular the recognition of complex interactions with the most prevalent esophageal disorder, gastroesophageal reflux disease (GERD). Heterogeneity in the clinical presentations of affected children and adults has created difficulties with uniform inclusion criteria and the development of disease-specific, patient-reported outcome (PRO) instruments. Furthermore, controversies regarding the appropriate therapeutic endpoints of EoE have impeded the design of clinical trials. Despite these obstacles, collaborative efforts by investigators, industry, the FDA, and patient advocacy groups have resulted in substantial progress in drug development in EoE over the past 2 decades.[3] The purpose of this article is to summarize discussions on EoE based on the 2016 Drug Development Conference sponsored by the Center for Diagnostics and Therapeutics of the American Gastroenterological Association.

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Diagnostic Criteria: Appreciating the Complex Interactions With Gastroesophageal Reflux Disease

The issue of how to differentiate EoE from GERD has confounded clinicians and researchers alike, and anyone attempting to design a clinical trial for EoE must confront this problem. To fully appreciate the issue requires some historical perspective. In 1982, it was reported that eosinophils in the esophageal squamous epithelium could be a manifestation of GERD.[4] Pathologists rapidly accepted this notion, and it became a common clinical practice for them to attribute esophageal eosinophilia to GERD. The first report describing EoE as a unique, clinicopathologic syndrome distinct from GERD was published in 1993.[1] After that, clinicians slowly began to appreciate that some patients who had esophageal eosinophilia attributed to GERD, but who did not respond to conventional GERD treatments, such as proton pump inhibitors (PPIs) and fundoplication, in fact had EoE.[5] As awareness of EoE grew, and physicians learned that GERD and EoE could have very similar clinical and histologic manifestations, much attention focused on how to differentiate the 2 disorders.

Early on, a trial of PPI therapy seemed the most logical and convenient means to differentiate GERD and EoE.[6] This practice was based on the assumption that gastric acid inhibition was the only important action of PPIs, and so only an acid-peptic disorder like GERD could respond to them. Accordingly, in 2007, a consensus report from the American Gastroenterological Association Institute defined EoE as a primary clinicopathologic disorder characterized by esophageal symptoms, esophageal biopsies showing $\geq$15 eosinophils per high-power field, and the absence of pathologic GERD as evidenced either by normal esophageal pH monitoring or lack of response to PPIs.[7] This definition implied that EoE and GERD were mutually exclusive disorders that could be distinguished by a trial of PPI therapy.

Soon after publication of the 2007 consensus report, it became apparent that its definition of EoE would require revision. Clinicians began to accept that patients could have both EoE and GERD simultaneously, and plausible reasons were proposed to consider that these disorders might interact in such a way that one could contribute to the development of the other.[8] In response to these and

Abbreviations used in this paper: **EoE, eosinophilic esophagitis; EREFS, EoE Endoscopic Reference Scoring system; FDA, Food and Drug Administration; FLIP, functional lumen imaging probe; GERD, gastroesophageal reflux disease; IL, interleukin; PPI, proton pump inhibitor; PRO, patient-reported outcome; PPIREE, proton pump inhibitor responsive esophageal eosinophilia; Th2, T-helper 2.**

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other revelations, in 2011 another group of experts chose to define EoE as "a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation."[9] This definition focused on what EoE was (an antigen-driven disorder) rather than on what it was not (GERD).

The recent recognition of a condition called PPI-responsive esophageal eosinophilia (PPI-REE) has added yet another wrinkle to the GERD versus EoE saga.[10] Patients with PPI-REE have typical EoE symptoms and EoE esophageal histology, they do not have endoscopic evidence of reflux esophagitis or abnormal esophageal acid exposure by pH monitoring, and they nevertheless exhibit a clinical and histologic response to PPI therapy. Indeed, studies have documented that 23%–61% of patients with symptomatic esophageal eosinophilia respond to PPI treatment.[11] Early reports attributed PPI-REE to subclinical GERD that responded to the acid-inhibitory effects of PPIs. However, recent studies have shown that the clinical, endoscopic, histologic, and esophageal gene expression features of PPI-REE and EoE are virtually identical, and multivariate analyses have not identified any feature that can distinguish PPI-REE from EoE.[12] Thus, PPI-REE resembles EoE far more than it resembles GERD. Recent data on the pathogenesis of EoE and GERD suggest how PPIs might benefit both disorders.

The pathogenesis of EoE is thought to start when a food antigen activates the immune system of a genetically susceptible individual, causing naive $CD4^+$ T cells to differentiate into T-helper 2 (Th2) cells that secrete Th2 cytokines, such as interleukin (IL) 5 (important for eosinophil production, activation, and recruitment), IL4, and IL13 (which stimulate esophageal epithelial cells to produce eotaxin-3, a potent eosinophil chemoattractant).[13] In this way, a food triggers an allergic response culminating in esophageal production of a chemoattractant that draws activated eosinophils to the esophagus, where they release noxious eosinophil secretory products that cause esophageal symptoms, damage, and remodeling. Recent studies suggest that the pathogenesis of esophageal injury in GERD also is primarily cytokine-mediated.[14,15] Rather than the traditional notion that refluxed acid causes a chemical injury that destroys esophageal cells, these recent studies suggest that esophageal damage in GERD is caused by inflammatory cells attracted to the esophagus by cytokines produced by esophageal epithelial cells when they are exposed to refluxed acid and bile.

In vitro studies using esophageal epithelial cells in culture have revealed anticytokine effects of PPIs that could contribute to the healing of both GERD and EoE, and that are entirely independent of effects on gastric acid production. Omeprazole, in concentrations readily achieved in blood with conventional dosing, has been shown to block eotaxin-3 secretion stimulated by Th2 cytokines in esophageal epithelial cells from patients with EoE.[16,17] Through this acid-independent, anti-inflammatory effect of blocking esophageal production of an eosinophil chemoattractant, PPIs might decrease esophageal eosinophils and symptoms in patients with EoE. In another series of experiments, esophageal epithelial cells from patients with GERD were found to secrete IL8 (a major mediator of inflammation) after exposure to acid and bile salts, an effect that also was blocked by omeprazole.[18] In addition to the well-known acid-inhibitory effects of PPIs, this acid-independent, anti-inflammatory PPI effect might contribute to GERD healing.

At least 3 possible explanations for PPI-REE emerge from these recent reports. First, patients with PPI-REE might have subclinical GERD as the sole cause of their esophageal eosinophilia, and their subclinical GERD responds to acid-inhibitory and, perhaps, anti-inflammatory effects of PPIs. A second possibility is that patients with PPI-REE have an antigen-driven esophageal eosinophilia (ie, they have EoE) without GERD, and the antigen-driven eosinophilia responds to PPI anti-inflammatory effects. The recent description of patients with typical EoE signs and symptoms who responded to a 6-food elimination diet and to PPI therapy (administered at different times) provides some support for this mechanism.[19] A third possibility is that patients with PPI-REE have subclinical GERD that is exacerbating or causing an antigen-driven esophageal eosinophilia, perhaps through GERD effects on esophageal barrier function that render the epithelium permeable to food antigens.[20] Such patients might respond to both the antisecretory and anti-inflammatory effects of PPIs. Because the PPIs have multiple effects that might benefit both EoE and GERD, a clinical and/or histologic response to PPIs does not rule in GERD, and should not rule out EoE.

The previously reviewed information suggests that the current focus on how to distinguish EoE from GERD might be counterproductive, because the 2 diseases often coexist with complex interactions. Even in the absence of GERD, it seems clear that some patients who have an antigen-driven esophageal eosinophilia can respond to PPI therapy. Although the mechanisms underlying the response of esophageal eosinophilia to PPIs remain unclear, it may be counterproductive to limit the diagnosis of EoE only to patients who fail to respond to PPIs. This practice creates an artificial disease category (PPI-REE) that is excluded from clinical trials and diverts attention from the primary, antigen-driven disease process. A focus on elucidating mechanisms whereby GERD can contribute to EoE pathogenesis might be more productive for achieving future advances in the treatment of this allergic disorder.

Targeting Patient Populations in Eosinophilic Esophagitis: Distinct Concerns Confronting Drug Development in Pediatrics

Several differences exist in how therapeutic success is measured in children and adults during a clinical trial.

For instance, for the evaluation of inflammatory bowel diseases, the Pediatric Ulcerative Colitis Activity Index was developed to account for school attendance, a factor that may not be present in adults. Such is the case with the current state of studying children and adults with EoE, especially as it relates to symptom assessment. In contrast to the relatively straightforward clinical presentation of adults with EoE, symptoms associated with EoE in children can vary according to age, are nonspecific in nature, and may be difficult to quantify.[21]

With respect to age, a young child may present with feeding dysfunction, a school-age child with reflux-like symptoms, and an adolescent with intermittent dysphagia. Whether these symptoms are reported differently by parents or patients may relate to developmental stage of the child, ability to cope with the underlying problem, or lack or of recognition by parents and family. For instance, a toddler may not be able to report swallowing problems specifically but would refuse to eat solids or not transition to more textured foods. This could be viewed by a parent as a behavioral problem as opposed to a manifestation of underlying esophagitis.[22] In contrast, an adolescent may report the occurrence of solid food dysphagia with steak once a month because of coping mechanisms of avoiding eating steak, chewing food for long periods of time, or drinking copious amounts of water. In the context of a clinical trial, these symptoms may not occur regularly enough to allow for a feasible clinical trial. In addition, these types of differences may necessitate a variety of types of validated patient/proxy-reported outcome measures to assess for therapeutic efficacy in young and older children.

The lack of symptom specificity creates problems in identifying children to target for enrollment and in identifying best PROs to measure symptoms. As opposed to adults who present with stereotypical features of solid food dysphagia and food impaction, young children often present with commonplace problems, such as feeding problems, spitting up or vomiting, abdominal pain, or symptoms that are only captured during thorough review of symptoms because they are related to coping.[22] Feeding problems may be reported as refusal to eat, disruptive mealtimes because of leaving the table, prolonged meals, or lack of progression to more advanced food textures or bite size. Reports of spitting up or vomiting may be indistinguishable from what may be reported with the more commonplace GERD. Abdominal pain typically occurs in the upper abdomen but is nonspecific. An astute physician may uncover coping mechanisms, particularly in highly atopic patients or those who have a family history of EoE, such as prolonged mealtimes caused by excessive chewing; avoiding highly textured foods, such as rice, bread, and steak or meats; or not eating at school or with friends because of fear of embarrassment. Because these symptoms are either very commonplace or may not be reported, targeting enrollment can be difficult. In addition, the lack of validated EoE PROs to measure these kinds of symptoms has created a vacuum for monitoring therapeutic efficacy. In fact, use of PROs developed for other diseases, such as reflux, may not be appropriate for EoE. Recent development of pediatric proxy and patient PROs specifically validated in pediatric EoE will clearly facilitate this process.[23–25]

Once suspected patients are identified, clinical trials may also be more complicated in children because of the need to perform sedated endoscopy and biopsy to assess for mucosal inflammation. Although an overall safe procedure, endoscopic assessments in children often require general anesthesia. Recent concerns have been raised about the potential consequences of repeated anesthetic exposures on the developing brain. In addition, risks of sedation and the procedure itself, time away from school for the patient and parent from work, and the psychological effect of endoscopies on children may make clinical trials in children more challenging than adults.

Treatment of Eosinophilic Esophagitis: Current Status of Drug Development

Although several treatments have been shown to be effective in EoE and are recommended in guidelines and clinical algorithms,[26] there are currently no FDA-approved medications for EoE. Because of this, all medications for this condition are presently being used off-label. This leads to difficulty with obtaining insurance coverage for medications and increased expense for patients. Moreover, medication formulations designed for airway indications are being suboptimally modified for esophageal delivery in EoE.

The mainstay of EoE pharmacologic therapy, for patients with esophageal eosinophilia who do not respond to PPIs, are topical corticosteroids. These are asthma preparations, such as fluticasone in a multidose inhaler or slurry of aqueous budesonide that is swallowed rather than inhaled to coat the esophagus. The efficacy of these medications has been shown in cohort studies,[27–29] randomized trials,[30–37] and several meta-analyses.[38–41] However, histologic nonresponse rates range from 25%–50% in randomized clinical trials,[30,32–37] and can be higher than that in studies that report "real world" rates.[42,43] One likely explanation for these high rates of nonresponse is that the topical steroids used in EoE are not formulated for esophageal deposition. Patients either have to coordinate puffing an inhaler into their mouth during a breath hold before swallowing a medication, or mix a thickened budesonide solution themselves. Either option is not ideal and leads to dosing and concentration inconsistencies. The importance of maximizing esophageal deposition was shown in 1 randomized trial where increased esophageal contact time, regardless of the delivery mechanism, was associated with improved histologic response.[36]

Acknowledging this engineering problem, there have been 2 recent phase 2 trials studying novel steroids specifically formulated to enhance esophageal deposition in EoE. In the first, 2 doses of a budesonide effervescent tablet and a budesonide viscous suspension were compared with placebo.[44] Histologic response rates ranged from 95%–100% for the topical steroids, compared with 0% in placebo. Although endoscopic severity was significantly decreased in the active treatment arms, both the active and placebo groups had a similar improvement in symptoms. In the second, a budesonide oral suspension was compared with placebo.[45] Here, 39% in the budesonide arm had a histologic response compared with 3% in placebo, but there were associated symptomatic and endoscopic improvements in these patients, measured for the first time using validated instruments. Both of these agents are currently in phase 3 trials and show the importance of developing medications to maximize esophageal deposition, but also of including specific study design elements that enhance measurement of the primary endpoints.

Until such new drugs are available, however, patients and physicians have reported several ways to increase topical steroid esophageal deposition. For budesonide, efficacy has now been reported for mixing a slurry of aqueous budesonide with sucralose, elemental formula, honey, maple syrup, agave nectar, rice cereal, xanthan gum, and several other similar thickening agents.[43,46–48] It is also possible to order compounded budesonide syrup from a specialized pharmacy. For fluticasone, using the diskus device rather than the multidose inhaler may be preferable. Inside the diskus is a strand of blister packets containing powdered fluticasone, which when opened, placed on the tongue, and swallowed, also improve esophageal eosinophil counts.[49] Use of other topical steroids, including ciclesonide, which is a high-potency steroid prodrug that must be activated by an epithelial esterase (present in both the pulmonary and esophageal mucosa), has also been reported.[47,50,51]

It is important to note that multiple other existing pharmacologic treatment modalities have been assessed for EoE. In general, these approaches are either not effective or limited by side effects. These strategies include systemic corticosteroids[29,31,52]; leukotriene antagonists[50,53–56]; mast cell stabilizers[54,57]; immunomodulators[58]; and biologics, such as anti-IgE and infliximab.[59–61]

With increasing knowledge of EoE pathogenesis, however, there is significant interest in developing treatments targeting the underlying physiology of EoE. The anti-IL5 medications were the first such agents tested in EoE, and there has been 1 small randomized trial in adults and 2 larger ones in children.[62–64] Although these agents resulted in a moderate decrease in esophageal eosinophilia, symptoms improved similarly in the placebo and active treatment arms in the 2 larger trials. Although in retrospect this lack of symptom benefit was likely caused by the use of nonvalidated instruments and other study design elements (see later), these medications are not currently being pursued for approval in EoE. However, both medications (mepolizumab and reslizumab) have been recently approved for treatment of eosinophilic asthma; use in EoE would be considered off-label.

Recently, there have been promising data regarding anti-IL13 medications. This class was first reported in a small randomized controlled trial, and showed efficacy for reducing esophageal eosinophil counts.[65] Phase 2 data from a different anti-IL13 antibody were recently presented.[66] In this randomized controlled trial, the medication significantly and markedly decreased eosinophil counts compared with placebo, significantly improved endoscopic severity, and there was also a strong trend toward symptom improvement.

In addition to these drugs, there are other studies listed on clinicaltrials.gov exploring novel agents in EoE. For example, an anti-IL4 antibody, dupilumab, is currently in phase 2 testing. Immunosuppressants (sirolimus) and a transforming growth factor-β inhibitor (losartan) are in proof-of-principle testing. A small molecule, which is an antagonist to the chemoattractant receptor-homologous molecule expressed on Th2 cells and blocks binding of prostaglandin D_2, has also shown promise.[67]

In summary, there are huge needs related to pharmacologic therapy of EoE. There are no FDA-approved medications, no available medications are formulated for esophageal deposition or target EoE pathogenesis, and nonresponse to primary and secondary treatments is common. However, there are also huge opportunities for drug development in EoE. Multiple new medications are under study, including novel topical steroid formulations, novel biologics, and novel small molecules. With the development of new validated outcome measures for EoE and incorporating specific clinical trial design elements, there is a higher likelihood of identifying effective medications.

Clinical Trial Design in Eosinophilic Esophagitis: Defining Endpoints

Identification of appropriate therapeutic endpoints is of central importance to clinical practice, investigator studies, and pharmaceutical trials. The ideal endpoints of therapy in EoE should be associated with a clinically meaningful reduction in symptoms, normalization of quality of life, resolution of esophageal inflammation, reversal of existing disease complications, and prevention of future complications.[68] In clinical practice, management decisions in EoE are often based on patient symptoms, whereas in clinical trials, histopathology as assessed by esophageal mucosal eosinophil density, is a primary determinant of efficacy. Current pharmaceutical trials being reviewed by the FDA are using the coprimary

endpoint of symptom assessment and eosinophilic inflammation. Additional endpoints of endoscopic activity and novel biomarkers of disease activity and pathogenesis are under development.

Symptom Endpoints

Initial investigator-initiated clinical studies in pediatric and adult EoE used "home grown" symptom assessment tools, physician or patient global assessment metrics, or dysphagia instruments previously validated in non-EoE cohorts. Over the past 5 years, several PRO instruments have been developed and validated for evaluation of symptoms and quality of life in both pediatric and adult EoE (Table 1). The Daily Symptom Questionnaire was developed and validated in the context of a pharmaceutical phase 2 study of budesonide oral suspension.[69] At the time of the design of this study, a validated PRO did not exist for assessment of dysphagia in EoE. The items of the Daily Symptom Questionnaire were developed based on patient focus groups to assess the frequency and intensity of dysphagia. Responsiveness to change in the context of a placebo-controlled trial of budesonide oral suspension demonstrated the ability of the instrument to detect change in symptom activity.[45] A second PRO instrument, the EoE Activity Index, was developed and validated for use in adults by an international collaboration led by a Swiss group.[70] In addition to questions about the frequency and intensity of dysphagia, the EoE Activity Index incorporated a novel, "visual dysphagia questionnaire" that asks patients about food avoidance and modification behaviors. The visual dysphagia questionnaire specifically takes into account that patients may not report dysphagia due to avoidance of harder texture foods such as meat or bread. In addition, slower eating patterns or modification of food particle size or consistency prior to ingestion are assessed to capture a more comprehensive view of dysphagia severity. A pediatric symptom assessment tool has been validated but not yet evaluated in terms of responsiveness to therapy.[23] Furthermore, quality-of-life instruments have been developed and validated for children and adults with EoE but performance in terms of responsiveness the therapy are still being evaluated.[24,71,72]

Although symptom assessment is a logical endpoint for trials in EoE, it is important to appreciate limitations to this outcome metric (Table 2). Symptoms of dysphagia are highly dependent on eating behaviors. Careful mastication, prolonged meal times, and food avoidance can circumvent dysphagia and lead to inaccurate assessment of disease activity. Even with incorporation of the visual dysphagia questionnaire, the EoE Activity Index was shown to have only modest detection of inflammatory or endoscopic activity.[73,74] Another major conceptual concern with overreliance on symptom outcomes is the relationship between symptoms and esophageal remodeling. Remodeling in the form of esophageal strictures, and not mucosal inflammation, is the major determinant of symptom outcomes of food impaction.[75,76] The current understanding of the pathogenesis and natural history of EoE posits esophageal remodeling as a long-terms consequence of esophageal inflammation.[77] Fibrostenotic strictures seem to have limited reversibility with therapeutics directed at the inflammatory response. Thus, holding anti-inflammatory therapies to the "high bar" of symptom improvement may overlook potential benefits of such therapies in preventing disease remodeling consequences. This view is supported by the clinical observation that symptoms of dysphagia can be effectively ameliorated in more than 90% of patients with esophageal dilation, without altering the underlying inflammatory response.[78] Similarly symptoms may persist in the setting of fibrotic strictures, in spite of normalization of mucosal inflammation. Other practical limitations of symptom assessment in clinical trials include the sporadic nature of dysphagia events that may not be captured with short-duration assessment windows and a substantial placebo effect that can make detection of meaningful symptom improvement challenging.[45]

Histologic Endpoints

Histologic assessment by means of eosinophil density is the most commonly used primary endpoint in current clinical trials in EoE (Table 2). The response is most commonly defined by a reduction in tissue eosinophilia. However, the optimal degree of reduction is poorly defined such that a variety of endpoints have been used including thresholds of <15, <10, <6, and <5 eosinophils per high-power field. Variations in the cross-sectional area of different microscope manufacturers is a concern when comparing values across different studies but this limitation can be corrected by normalizing density to eosinophils per mm^2.[44,79] Most clinical trials have used a central, blinded pathologist to improve consistency. The calculation of peak eosinophil counts can be based on sampling of multiple levels of the esophagus or the mean of multiple high-power fields

Table 1. Patient-Reported Outcome Instruments for Children and Adults With EoE

Symptom scoring tool[98]
Dysphagia Assessment Tool[34]
Physician global assessment
Patient global assessment
Mayo Dysphagia Questionnaire
EoE Quality of life in adults[a71]
Dysphagia Symptom Questionnaire[a69]
Pediatric EoE Symptom Severity[a23]
Pediatric quality of life[a24]
EoE Activity Index[a70]

[a]Validation in EoE.

Table 2. Advantages and Disadvantages of Therapeutic Endpoints in EoE

Endpoint	Advantages	Disadvantages
Symptoms	Addresses FDA guidance regarding patient perspective, intrinsic to disease definition, validation of specific PROs	Dependent on eating behavior and food modification, sporadic basis of complaints, differences in pediatric and adult symptoms, association with esophageal remodeling rather than inflammation, placebo response
Eosinophil density (eosinophils/high-power field; eosinophils/mm^2)	Objective biomarker, highly reproducible, intrinsic to disease definition, applicable to both children and adults, responsiveness in placebo-controlled trials	Limited correlation with symptoms, heterogeneity in methods to quantify, threshold to define response not established, tissue sampling variability, incomplete measure of disease activity
Endoscopic features (EREFS)[89]	Objective measure, moderate-good interobserver agreement, responsiveness in placebo-controlled trials, measures "whole organ" activity, correlation with disease activity, applicable to both children and adults	Variability in prevalence of individual features, limited correlation with eosinophil density, threshold to define response not established
Quality of life[24,25,71]	Addresses FDA guidance regarding patient perspective, pediatric and adult instruments validated	Responsiveness to therapy not established, threshold to define response not yet defined, limited correlation with eosinophil density, not able to be used as a clinical trial primary endpoint
Comprehensive histologic assessment (composite index of multiple histologic parameters)[80]	Addresses concerns of overreliance on eosinophil density, applicable to both children and adults	Limited validation, responsiveness to therapy not established, variability in prevalence of individual features, reliance on tissue orientation
Esophageal distensibility (radiologic assessment or impedance planimetry)[76,96]	Objective measure of esophageal remodeling, correlation with symptom outcomes	Impedance planimetry not widely available, automated analyses under development, responsiveness to therapy not established
Gene expression[95]	Comprehensive assessment of multiple factors involved in pathogenesis	Clinical relevance of molecular readout not established, advantages over eosinophil density not established

showing the greatest density of eosinophils.[34] Additional studies have reported endpoints based on a percentage reduction in eosinophilia (ie, >50%, >90%) or mean eosinophil densities for a cohort.[32] Overlooked markers, such as expression of eosinophil activation products, basal cell hyperplasia, spongiosis, subepithelial fibrosis, lymphocytes, or mast cell infiltration, may be as relevant as the actual number of eosinophils. The recent development of an EoE Histologic Severity Score has included several of these additional pathologic parameters to provide a more comprehensive and hopefully more accurate characterization of mucosal inflammation in EoE for clinical trials.[80] However, histologic improvement of mucosal inflammation could be misleading as an indicator of overall disease activity. Studies have demonstrated that esophageal eosinophilia can extend to involve the submucosa and muscularis layers that are not sampled by esophageal mucosal biopsies.[59,81–83] Pediatric and adult studies in EoE using endoscopic ultrasonography revealed significant expansion of the esophageal wall and the individual layers including the mucosa, submucosa, and muscularis propria compared with healthy control subjects.[83,84]

Advantages of histologic assessment of EoE activity using esophageal mucosal eosinophil density include that it is an objective and quantifiable measure with a high degree of interobserver agreement.[85] Controlled trials have demonstrated a very low placebo response for eosinophil density over 2-to-16-week study periods. Reduction in eosinophil density has generally tracked with improvement symptom and endoscopic outcomes, although the degree of concordance has been variable and limited across trials.[38,74]

Problems with the use of eosinophil density as the primary outcome of EoE trials are based on the limited correlation with symptom outcomes.[74,86] This observation has led to concerns that other markers of inflammation other than eosinophil density may be factors in disease activity and progression.[80] Eosinophil degranulation proteins including eosinophil-derived neurotoxin, eosinophil peroxidase, and eosinophil cationic protein may identify eosinophil activity that may be as relevant a metric as eosinophil density.[80,87] Additional inflammatory cells, such as lymphocytes, basophils, and mast cells, have defined roles in the allergic and Th2 pathogenesis of EoE and are not captured with the current focus on eosinophil density.[88] Eosinophil quantification in the esophageal mucosa does not evaluate subepithelial remodeling that has been associated with adverse symptom outcomes. Use of the Histologic Severity Score may provide a more comprehensive assessment of mucosal inflammation. Further studies linking eosinophil

density with disease progression will also substantiate the current reliance of this biomarker as a primary endpoint.

Endoscopic Outcomes

The EoE Endoscopic Reference Scoring system (EREFS) is a classification and grading system designed to standardize nomenclature for the major endoscopically identified, esophageal features of EoE (edema, rings, exudates, furrows, and strictures).[89] Studies from the United States and Europe have demonstrated moderate to good interobserver and intraobserver agreement using EREFS.[89,90] Kappa scores for interobserver agreement exceeded that of the LA classification system for GERD. Prospective use of the EREFS system has identified endoscopic detection of esophageal abnormalities in more than 95% of patients with EoE.[45,91] Recent studies have demonstrated the clinical relevance of endoscopic severity assessment in EoE. The severity of each of the EREFS subscores was associated with patient-reported global symptom activity.[70] Food impaction risk and esophageal mural distensibility was also significantly associated with EREFS ring severity.[92] Moreover, physicians' global assessment of disease activity is largely based on endoscopic findings, rather than severity of histopathology.[73]

A recent study demonstrated that the EREFS score had a high degree of accuracy for diagnosis of EoE and significant responsiveness to treatment.[93] This study prospectively evaluated patients with EoE who were treated with either topical steroids or dietary elimination and compared their endoscopic findings with control subjects without EoE. EREFS correctly identified patients with EoE with a high degree of accuracy, with an area under the receiver operator characteristic curve of 0.934, sensitivity of 88%, specificity of 92%, positive predictive value of 84%, and negative predictive value of 94%. Another recent study was the first randomized, placebo-controlled trial to incorporate endoscopic outcomes determined by EREFS.[45] In this study, EREFS scores significantly improved after treatment with budesonide oral suspension and remained unchanged with placebo. Each of the individual EREFS subscores (ie, edema, rings, exudate, furrows) significantly improved as did overall scores for the proximal and distal esophagus.

In summary, a growing body of literature supports the validity of systematic evaluation of endoscopic features, as measured by the EREFS, with a promising role as treatment endpoint in clinical practice and therapeutic trials (Table 2).[91] The ability of medical and diet therapies to significantly improve endoscopically visible esophageal inflammatory and structural alterations substantiates the improvements in symptoms and histopathology. The emerging role of endoscopic assessment in EoE has noteworthy parallels with the emphasis on endoscopic mucosal healing as a primary endpoint of therapeutics in inflammatory bowel disease and GERD.

Future Endpoints

Biomarkers of EoE disease activity beyond symptoms and mucosal healing are being actively evaluated. mRNA expression provides a molecular fingerprint of key upregulated and downregulated genes in esophageal biopsies of EoE that is distinct from the signature identified in control subjects and patients with GERD.[94,95] The selection of a subset of 96 genes signature profile termed the Eosinophil Diagnostic Panel includes clusters of genes that depict the Th2 inflammatory response, mast cell activation, and fibrosis pathways. Reversal of the EoE pattern has been demonstrated in the setting of randomized controlled trials using both topical fluticasone in children and anti-IL13 therapy in an adult study.[33,65] In addition to providing a biomarker panel for disease activity, the Eosinophil Diagnostic Panel offers potential for examining molecular pathways that may provide insights into the pathogenesis and inform a personalized approach to the therapy of EoE.

At the other end of the spectrum, end organ assessment of esophageal remodeling of EoE is being evaluated with the functional lumen imaging probe (FLIP). FLIP is a catheter-based technology that provides information about the biomechanical properties of the esophagus. The device uses impedance planimetry to provide detailed measurement of the esophageal wall cross-sectional area in response to incremental pressure using controlled, volumetric distention. In an initial study, FLIP demonstrated a 50% reduction in esophageal distensibility in EoE compared with control subjects using a metric defined as the distention plateau (cross-sectional area or diameter at which incremental pressure yields minimal changes in diameter).[96] In a follow-up study, the distention plateau was shown to be significantly reduced in patients with EoE with adverse outcomes of food impaction.[76] Thus FLIP may provide a quantitative measure of esophageal remodeling in EoE that is a major determinant of symptom outcomes. As such, FLIP may be a clinically relevant biomarker of remodeling that complements the use of mucosal inflammation endpoints.[97] The use of FLIP to measure esophageal distensibility is being examined as a secondary endpoint of therapeutic trials in EoE.

Conclusions

The past 2 decades have witnessed remarkable progress in the development of pharmacologic therapies in EoE. Clinical and translational research has refined the diagnostic criteria and continued to validate disease-specific, PRO instruments. Unique biomarkers that address the immunologic basis and remodeling

consequences of EoE are being established as novel endpoints of disease activity while providing valuable insights into pathogenesis. Investigator- and industry-sponsored clinical trials have paved the way for appropriate study design in EoE. The field has evolved from case series to randomized, controlled trials of topical steroids optimized for esophageal delivery and targeted biologic therapies that address the immunologic underpinnings of the newest esophageal disease. Ongoing collaborative engagement of clinicians, investigators, industry, the FDA, and patient advocacy groups is essential for continued progress in therapeutics in this relatively new yet rapidly growing esophageal disease.

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Conflicts of interest

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